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--32. (New) A pharmaceutical formulation, according to Claim 1, for intranasal administration comprising morphine or pharmaceutically acceptable salt thereof at a pH from about 5.0 to about 6.0.--

REMARKS

Claims 16-29 have been cancelled as being drawn to a non-elected invention. New Claims 30-32 have been added. Accordingly, Claims 1-15 and 30-32 are pending in this application.

The present invention provides pharmaceutical formulations for the intranasal administration of morphine or a morphine salt at a pH range of from about 3.0 to about 7.0. As stated by the expert in the accompanying 37 C.F.R. § 1.132 Declaration, it would have been surprising that the intranasal administration of morphine at such a pH range is useful. More specifically, as stated by the expert, it has been a common teaching in the art that the degree of ionization of a drug, in particular intranasal drugs, influences the absorption potential of the drug into the blood stream. It has been believed that as the portion of a drug in its ionized state increases, the absorption potential of the drug decreases. The degree of ionization of a drug is largely determined by the drug's dissociation constant, the *pKa*, and the pH of the solution in which the drug is dissolved. A basic drug would be mostly in its unionized state when dissolved in a solution with a pH that is greater than the *pKa* of the drug. Accordingly, basic drug formulations are believed to be best absorbed from alkaline solutions with the pH of the solution greater than the *pKa* of the basic drug. Morphine is a basic drug with a *pKa* of about 8. Accordingly, it has been believed that morphine would be best absorbed when formulated in a basic solution since in such a formulation most of the morphine would be in its unionized state. However, the present invention surprisingly shows that there is a high level of morphine absorption into the bloodstream in the pH range from about 3.0 to about 7.0.

Rejections under 35 U.S.C. §102(b) and (e)

Claims 1-5 and 7 are rejected as being anticipated by Hussain et al., U.S. Patent 4,464,378. More specifically, the Office Action states that Hussain et al. teach "a pharmaceutically acceptable nasal dosage form for nasally delivering systemically therapeutic levels of drug e.g., morphine, to a warm blooded animal ...[at] 15mg /0.1 ml solution (15%) morphine at pH 4.5." (Office Action, page 4, second ¶.) Applicants traverse this rejection.

In order for a prior art reference to anticipate a claim, the prior art reference must teach every element of the claim. The disclosure by Hussain would not have taught a skilled artisan an intranasal pharmaceutical formulation containing morphine at a pH of 4.5, as asserted by the Examiner.

In particular, Hussain does not explicitly state that his morphine sulfate solution is administered at a pH of 4.5. Hussain simply states that "The procedure described above is substantially repeated, expect that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride..." (Col. 10, Lines 45-49.) Hussain describes several steps in the procedure of making nalbuphine hydrochloride. The adjustment of the pH to 4.5 is one step in the procedure.

We submit herewith a Declaration under Rule 132 by Dr. Charanjit R. Behl, an expert in the field of drug delivery systems. In the Declaration, Dr. Behl states that a skilled artisan would not have been certain if the adjustment of the pH was to be repeated for the morphine sulfate solution. Moreover, the expert states that there are several reasons why a skilled artisan would have believed that Hussain does not teach adjusting the pH of the morphine sulfate solution to a pH of 4.5.

Firstly, as the expert states in the Declaration, a skilled artisan would not have taken the disclosure of Hussain with respect to morphine sulfate seriously. In particular, Hussain describes his morphine sulfate solution as containing 15mg of morphine sulfate per 0.1ml of water. However, the expert states that this result of Hussain cannot be reproduced. In particular, the expert states that contrary to the teaching of Hussain, the solubility of morphine sulfate in water is **not** 150 mg/ml at any pH. (According to the expert, the solubility of morphine sulfate at a pH of 4.5 is 53.8 mg/ml.)

Secondly, the expert states in the Declaration that the procedure outlined by Hussain for nalbuphine hydrochoride would not provide a morphine sulfate solution with a pH of 4.5. More specifically, Hussain teaches to combine 15 grams of nalbuphine hydrochloride with 80 ml of water, and to add enough sodium hydroxide solution to bring the pH of the composition to 4.5. According to the expert:

> [T]he resultant pH of morphine sulfate solution would not be 4.5 by following the outlined procedure. According to the Merck Index, morphine sulfate solution has a pH of about 4.8. Thus, the addition of the sodium hydroxide solution to the morphine sulfate solution would bring the pH of the morphine composition up, not down. (Page 4, First paragraph.)

Since the description by Hussain cannot be followed to attain a morphine sulfate solution of 4.5, Hussain does not describe the pH for the morphine sulfate solution.

Therefore, the Applicants respectfully maintain that Hussain does not teach every element of the claimed invention. Accordingly, withdrawal of this rejection is respectfully requested.

Additionally, Claims 1-11 and 14-15 are rejected as being anticipated by Merkus 5,756,483 under §102(b) and as being anticipated by Merkus 5,942,251 under §102(e). More specifically, the Office Action states that both these patents teach:

> a pharmaceutical solution formulation of morphine for nasal delivery employing a morphine pharmaceutical salt at a pH of 6, which also contains applicant's preferred other pharmaceutical excipients, including a preservative, a phosphate buffer, a humectant, and an absorption enhancing agent." (Office Action, Page 4, fourth Paragraph.)

Applicants respectfully traverse these rejections. The Merkus patents both have the same disclosure with respect to morphine. Both these patents teach away from using nasally-administered morphine at a pH of 6. In particular it is stated in Merkus:

> The exact dose which was delivered to the volunteers was 16 mg of morphine (range 15-18mg) and the bioavailability of morphine from this nasal spray was 26-35%. The bioavailability of morphine after oral application is estimated to be about 40%...This means, that the bioavailability of morphine after giving nasal spray is... relatively low. After nasal absorption there is no first pass effect and therefore the nasal

bioavailability should be higher than the oral. (5,756,483: Col. 6, Lines 54-64; 5,942,251: Col.7, Lines 14-22.)

Thus, Merkus teaches that the bioavailability of nasally-administered morphine is low. In fact, Merkus teaches that the bioavailability of nasally-administered morphine is lower than the bioavailability of orally-administered morphine. As stated by Dr. Behl in the accompanying Declaration, the first pass effect, inherent in oral administration, decreases bioavailability. In particular, due to the first pass effect, drugs absorbed via the gastrointestinal tract may be deactivated by digestive and liver enzymes. Therefore, one of the main objectives in administering a drug nasally is to avoid the first pass effect inherent in oral administration.

Accordingly, since Merkus discloses that nasally-administered morphine has lower bioavailability than orally-administered morphine, the disclosure by Merkus would have led a skilled artisan away from preparing and utilizing a nasally-administered morphine. Accordingly, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §103(a)

Claims 12-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Merkus 5,756,483. Applicants respectfully traverse this rejection.

In order for a *prima facie* case of obviousness to be made, a prior art reference must suggest or motivate a skilled artisan to modify the reference. Secondly, this suggestion or motivation must be accompanied by a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations.

Claims 12 and 13 are dependent claims that add to Claim 1 a thickening agent and a humectant, respectively, to be included in the intranasal morphine pharmaceutical formulation. The Merkus 5,756,483 patent clearly does not suggest or motivate a skilled artisan to modify their teachings to obtain the intranasal morphine pharmaceutical formulation of the present invention. To the contrary, as stated above, a skilled artisan would have been taught away from the present invention by the disclosure in the Merkus patents.

Accordingly, the present invention is not obvious in view of the Merkus patents. Accordingly, withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that the application, including Claims 1-15 and 30-32, are now in proper form for allowance, which action is earnestly solicited. If resolution of any remaining issue is required prior to allowance of this application, it is respectfully requested that the Examiner contact Applicants' undersigned attorney at the telephone number provided below.

Respectfully submitted,

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